Emerging Problems in Infectious Diseases

Influenza pandemics: a historical retrospect

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Keywords: influenza A, pandemic, H1N1, history

J Infect Dev Ctries 2009; 3(5):331-334.

Received 1 May 2009 - Accepted 24 June 2009

The recent global outbreak of human cases of swine origin influenza A (H1N1) has spread fear that this virus will be of pandemic proportions causing high morbidity and mortality. While it is too early to determine the pandemic nature of swine origin influenza A (H1N1), it may be useful to look at the history of influenza pandemics described since recorded history. The first well-documented outbreak that fits a description of a pandemic occurred in 1580, originating in Asia and sweeping through Europe, Africa, and the Americas along trade routes [1]. In Asia the local people gave it the name of "wind illness" to indicate the speed of propagation. Then, at intervals of roughly one to four decades, thirty-one influenza pandemics have occurred [2,3]: three over the past century in 1918-19, 1957, and 1968 (Fig.1); and six in the 19th century in 1800-1801, 1837, 1843, 1857, 1874, and in 1889-92. The latter was known as the "Russian flu" in Western Europe.

Beginning in May 1889 in Bokara, Central Asia, the Russian flu travelled quickly through Russia and Germany and then into Western Europe along the new rail networks [4]. While not having the severity of the so-called "Spanish flu" outbreak of 1918-19, the 1889-92 pandemic caused extensive morbidity and high general mortality with approximately 250,000 deaths in Europe [5] (Table1).

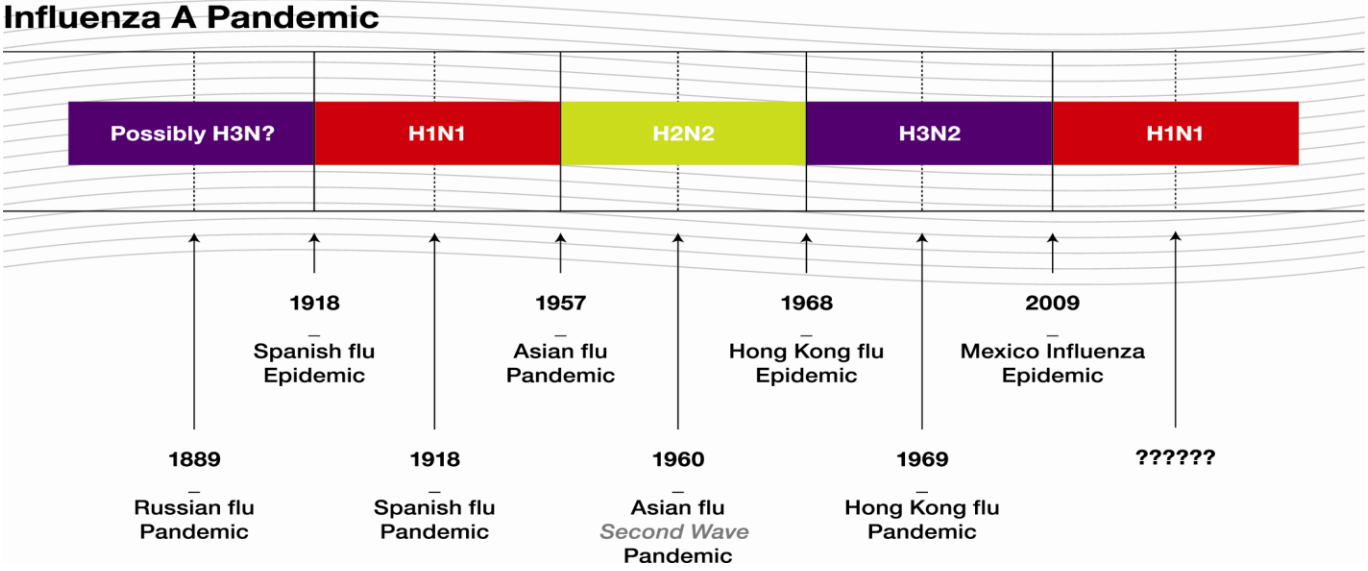
Table 1. Influenza pandemics deaths

1918	40-50 million deaths worldwide
1957	1-2 million deaths worldwide
1968	700,000 deaths worldwide

The most severe influenza pandemic in recorded history was the Spanish influenza. The disease swept through North America, Europe, Asia, Africa, Brazil and the South Pacific. It was exceptionally severe: an estimated one third of the world's population was infected. Case fatality rates were calculated at 2.5% compared to the previous influenza epidemics which were estimated at less than 0.1% [6]. In the United States, the Spanish flu caused a mortality rate of 0.3 percent (based on data from 24 states). In India, the mortality rate was extremely high at around 50 deaths from influenza per 1,000 people; in the Bombay region of India, mortality was thought to be at 6.2%. In the Philippines, the mortality rate was 2.8%. These data show how the case fatality rates varied in different parts of the world and demonstrate that it was disproportionately high in poor countries. A recent systematic analysis based on vital statistics predicts that if the same pandemic were to occur today, approximately 96% of deaths would occur in developing countries [7].

Contemporary reports published shortly after the pandemic say it caused an estimated 21-25 million deaths worldwide with about 550,000 in the United States; 2,163,303 in Europe; and 15,757,363 in Asia [8]. In recent years, estimates have risen, speculating that over 100 million deaths were caused by the Spanish flu, but this is probably exaggerated. Current estimates say 50 million to 100 million people worldwide were killed [9], while some American scientists suggest that the Spanish flu pandemic killed 40 or 50 million [1] (Table1). Most of the victims were young adults, a frightening element that is thought to be a feature of the swine-origin flu outbreak in Mexico [10]. The symptoms

Figure 1. Historical schematic of influenza pandemics over the past 150 years.



The timeline depicts the emergence of the past 4 Influenza pandemics and their proceeding epidemics. Two to three waves of the pandemic mortality were observed. Each pandemic was associated with H1, H2, or H3 Influenza subtype (3).

associated with the Spanish flu were unusually severe [11].

Most victims died of pneumonia caused by secondary bacterial infections, but evidence suggests the virus itself caused a form of pneumonia with extensive haemorrhaging and oedema in the lung that could kill within few days. At the post-mortem table, daunted pathologists found themselves faced with swollen lungs, grossly oversize spleens, pulmonary alveoli overflowing with albuminous exudate, and necrotic tissue [12].

Despite clinical and epidemiologic similarities to the influenza pandemics of 1889-1992 and even earlier, vast sectors of the medical world everywhere doubted if the Spanish flu was really influenza.

The aspecific nature of the symptoms and the variety of the clinical cases gave rise to a whole series of possible interpretations of the illness, including "trench fever", dengue, and anthrax. Intestinal complications also led doctors to believe it might be cholera or some other exotic disease. Certain forms, such as fulminating pneumonic infection with sub-cutaneous bleeding, even gave credence to the suspicion, mentioned in various medical journals, that this was an outbreak of the pneumonic plague [12]

The first wave of influenza appeared early in the spring of 1918 [9]. It did not have a particularly aggressive nature. Those who caught the flu had shivers and a temperature for three or four days, then got better. The illness therefore became known as "three-day fever." Later it took on the name of Spanish fever or simply Spanish flu, due to the false belief that the Iberian Peninsula had been the cradle of the disease; hence the disease went down in history with this name (Fig. 2-3).

Figure 2. Camp Furston, Kansas, 1918.

Hospital of Camp Furston, Kansas (now called Fort Riley), 1918.
Photo credit: Stanford University (http://virus.stanford.edu/uda/),

It was the so-called second wave, in the autumn of 1918, which was responsible for most of the deaths, due to an unusually severe, hemorrhagic pneumonia. Therefore it is still uncertain whether the first wave appeared in Europe or in America, and it must also be determined if links can be established

Figure 3. The face mask as countermeasure against the 1918-19 influenza epidemic.

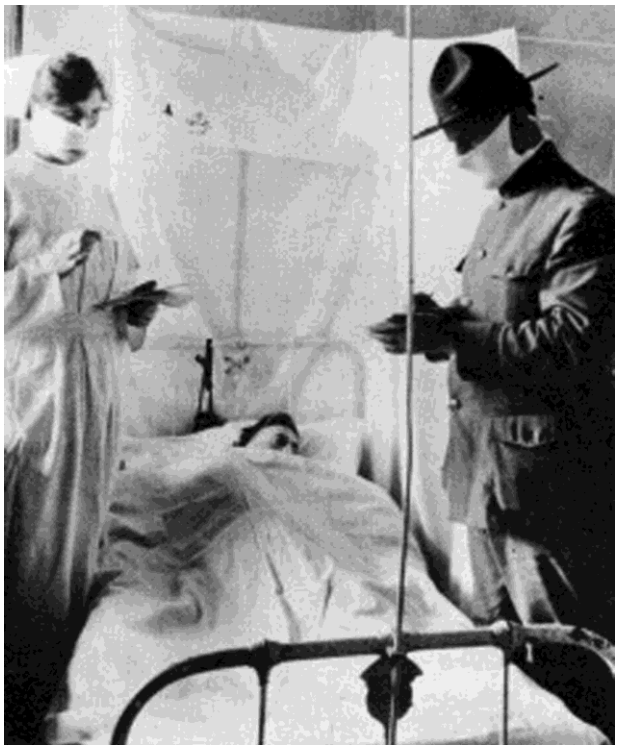


Photo credit: American Red Cross (http://www.redcross.org)

with previous epidemic waves, such as the Austria-Hungary wave of 1917. It is not clear if the lethal autumn wave appeared simultaneously in different regions of the world (France, Sierra Leone, and Massachusetts) [13] or if one must trust the prevailing opinion indicating the starting point of the second wave in Brest, France, on August 22, 1918. The studies seem to undervalue the mysterious link between the first and the second waves. In European countries, for example in England, where the first wave appeared later than in other countries, the second one behaved in the same way, also appearing later than the second wave in other countries; this element may lead one to suppose the existence of a progenitor virus, which continued spreading during spring and summer, undergoing modifications leading to increased pathogenicity and virulence. Italian official documents [14] reveal that the first cases of the second wave started in Italy not at the end of August, but in July, and this agrees well with the fact that Italy had the highest death rate in Europe. The first two deaths, due to "flu complications", were reported in the south of the country, in the clearing station where the troops departed and returned from the south-eastern front (Albania, Macedonia). Moreover, in Italy, as well as in England and in France, there was not a clear interruption between the first and the second waves. Hotbeds deriving from the first wave lasted throughout the summer, an anomaly reported by many medical journals, such as the *Lancet* [15]

Although the analysis of short fragments of RNA from the tissues of 1918 victims is now possible with new powerful molecular technologies [16], the cause of the 1918 virus's virulence is still not precisely known. The available data suggests that the virus was a human-avian reassortant which had entered the human population a short time (likely 6-12 months) before the beginning of the pandemic.

After the 1918 Spanish flu, there were two less severe pandemics which began in Asia and spread around the world [17,4]. In 1957, an H2N2 virus called "Asian Flu" appeared in China. It quickly swept through the population, replacing the previously circulating H1N1 virus. Similarly, in 1968, an H3N2 virus emerged from Hong Kong replacing the H2N2 virus. Within four weeks it had spread to Vietnam and Singapore. By September, the virus had reached the Philippines, India, northern Australia, the United Kingdom, continental Europe, and the United States. Japan reported its first cases of H3N2 in January of 1969, while South Africa and South America were spared until mid-1969. The Hong Kong Flu infected an estimated 1-3 million people around the globe. The H1N1 serotype resurfaced in 1977, and currently, H3N2, H1N1, and reassortant H1N2 viruses circulate in the human population.

In 1976, an H1N1 subtype caused a global alert [4-19] (Table 2). In January of that year, at Fort Dix, New Jersey, an Army recruit collapsed and died following a march. It was determined that he died of "swine flu," serotype H1N1, that was feared to be a direct descendant of the deadly virus of the 1918 Influenza Pandemic. Although he was the only death at the fort, the alarm led the government to promote a large national campaign of vaccination. By the end of the month, however, , investigators found that the virus had mysteriously disappeared after infecting some 500 soldiers. The feared pandemic, which some experts estimated at the time could infect 50-60 million Americans, never unfolded [18]. Only a few hundred cases of swine flu and one death were ultimately reported in the U.S. The panic in 1976 was partly because of the belief—now known

to be erroneous—that the 1918-19 flu pandemic was caused by a virus with swine components.

Table 2. Pandemic Threats in the 20th century.

1976: Swine Flu (H1N1)
1977: Russian Flu (H1N1)
1997: Avian Flu (H5N1)
1999: Avian flu (H9N2)

In 1997 and 1999, new versions of avian influenza crossed into humans in China and Southeast Asia, sparking fear of new pandemics. However, these strains to date are not easily transmitted from human to human, and outbreaks have been confined to a limited number of people.

Pandemics, in conclusion, have occurred several times in the past [19]. Virologists and public health experts foresee a new influenza pandemic in this century. The lessons of the past can be of crucial importance in planning effective control measures in case a pandemic with the magnitude of that in 1918 occurs again [20] .

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Conflict of interest: No conflict of interest is declared.